Arch Sex Behav (2014) 43:407–409
DOI 10.1007/s10508-013-0187-9

CLINICAL CASE REPORT SERIES

Bilateral Non-arteritic Ischemic Optic Neuropathy in a Transsexual Woman Using Excessive Estrogen Dosage

Katrien Wierckx · Julie De Zaeytijd · Els Elaut · Gunter Heylens · Guy T'Sjoen

Received: 1 November 2012 / Revised: 9 April 2013 / Accepted: 16 August 2013 / Published online: 21 September 2013

Abstract We present a case report on a 53-year-old transsexual woman who developed acute painless vision loss in both eyes during cross-sex hormone treatment. After 10 months of cross-sex hormone treatment, she experienced total vision loss of the right eye and, 6 months later, vision loss to 20/63 in the left eye. After a full ophthalmic exam, bilateral sequential non-arteritic ischemic optic neuropathy (NA-ION) was diagnosed. Extensive etiological work-up revealed no cardiac abnormalities or inherited blood-clotting disorders. A manifest self-administered overdose of transdermal estrogen treatment with serum estradiol levels of 5,765 pg/ml was possibly related to the sequential bilateral NA-ION resulting in nearly total vision loss in this transsexual woman.

Keywords Gender identity disorder · Transsexualism · Gender dysphoria · Non-arteritic ischemic optic neuropathy

Introduction

Gender identity disorder (GID) is defined as a significant incongruence between gender identity—the sense one has of being male, female or in between—and the sex assigned at birth. Treatment for adults often involves cross-sex hormone therapy and sex reassignment surgery. Cross-sex hormone treatment of transsexual women in our gender clinic consists of the administration of cyproterone acetate 50 mg, a derivative of 17-hydroxyprogesterone with strong antiandrogenic characteristics, combined with oral or transdermal estrogens, aiming at physiological substitution dosage (Wierckx et al., 2012). Safety data on estrogen use in natal men are scarce. In this case report, we present a transsexual woman who experienced nearly total vision loss likely associated with excessive transdermal estrogen use.

Case Report

A 53-year-old natal male was referred for diagnostic assessment of gender dysphoria. Mental health evaluation confirmed this diagnosis as well as mixed personality disorder with mainly cluster B traits (DSM-IV-TR codes 301.83, 301.50, and 301.81). As she had been impatient to start transition, cyproterone acetate 50 mg had already been prescribed by her general practitioner several weeks before first consultation with the endocrinologist. She had a history of type 2 diabetes, hypertension, obesity, and smoking. Her medical treatment included metformine 850 mg BID, glimepride 3 mg OD, and insulin therapy (NPH 12 Units OD). As there were relative contra-indications for cross-sex hormone treatment, we advised the addition of transdermal estrogens mildly dosed (17-β estradiol gel 2 mg daily TTS), along with a strong recommendation to adopt a healthier life style and to quit smoking.

During the first 6 months of follow-up, her physical health improved as she lost weight (−3.6 kg), quit smoking, and had a good glycemic control (HbA1c: 7.0 %). As hypertension persisted, lisinopril 20 mg OD was started. However, her mental condition remained fragile during that time. She was impatient

K. Wierckx (✉) · G. T'Sjoen
Department of Endocrinology, Ghent University Hospital, 6K12 I.E., De Pintelaan 185, 9000 Ghent, Belgium
e-mail: Katrien.Wierckx@ugent.be

J. De Zaeytijd
Department of Ophthalmology, Ghent University Hospital, Ghent, Belgium

E. Elaut · G. Heylens · G. T'Sjoen
Center for Sexology and Gender Problems, Ghent University Hospital, Ghent, Belgium

for feminization and was admitted several months at the Department of Psychiatry because of depression and personality problems.

After 10 months of cross-sex hormone treatment, she experienced total vision loss of the right eye and 2 months later she experienced a cerebrovascular accident at the left frontoparietal lobe with almost complete resolution afterwards. Six months later, she was admitted again to the emergency department due to vision loss to 20/63 in the left eye. Serial fundoscopy showed a swollen disc in both eyes in the acute phase, which evolved into pallor later. Diagnosis of bilateral non-arteretic anterior ischemic optic neuropathy was made. CT-brain revealed the older ischemic areas. Genetic testing for inherited blood-clotting disorders and cardiac work-up were negative. Serum estradiol levels of 5,765 pg/ml (guidelines: <200 pg/ml) were detected, reflecting excessive estrogen administration, and the patient admitted to overdosing with transdermal estrogen in order to enhance feminization. We recommended strict control of cardiovascular risk factors and complete stop of estrogen therapy.

Discussion

We describe the first case of bilateral non-arteretic anterior ischemic optic neuropathy, possibly related to the self-administered excessive estrogen treatment. It has been previously addressed that many transsexual women tend to overdose estrogen treatment (Gooren, Giltay, & Bunck, 2008). However, in our clinic, all patients are systematically informed that clinical feminization is achieved not immediately but over a period of 1–2 years and those results may be highly variable.

Non-arteritic ischemic optic neuropathy (NA-ION) is a well-recognized, visually disabling disease. The annual incidence of NA-ION has been estimated from 2.3 to 10.2 per 100,000 in persons 50 years and older (Johnson & Arnold, 1994). This condition is caused by an acute perfusion insufficiency leading to infarction of the optic nerve. Generally, a transient fall of blood pressure is assumed to be the main mechanism of NA-ION. As the autoregulation of the anterior part of the optic nerve has a narrow critical range, small changes in perfusion pressure make it vulnerable to ischemia. The available evidence suggests that NA-ION has a multifactorial etiology with ocular and systemic predisposing factors (such as hypertension, diabetes mellitus, atherosclerosis, etc.) and precipitating factors such as the natural fall in arterial tension at night, often aggravated by anti-hypertensive medication. Only occasionally, NA-ION is caused by a thromboembolic event (Hayreh, 2009). NA-ION usually has classical history and clinical signs, which makes it easy to diagnose (Hayreh, 2009).

In this patient, fundoscopic findings and cardiovascular comorbidity may fit with a hypotensive etiology. However, several other clues may also suggest a thromboembolic etiology or a combination of both. First, the severity for this patient was very high as this resulted in an almost total blindness without any recovery. Ocular damage due to transient nonperfusion or hypoperfusion results in much less severe and less extensive injury to the anterior part of the optic nerve than does damage caused by a thromboembolic event (Hayreh, 2011). Consequently, a spontaneous visual improvement is often observed in "classic" NA-ION whereas in contrast to an embolic NA-ION ONH damage is often permanent (Hayreh, 2011). Second, the involvement of the fellow eye after 6 months is quite unusual in "classic" NA-ION. Newman et al. (2002) observed in an observational study in 332 patients involvement of the fellow eye in 14.7 % of patients after a median follow-up of 5 years. Others found that involvement of the fellow eye by NA-ION occurred after a median time of 6.9 years in diabetics (Hayreh & Zimmerman, 2008a). On the other hand, in cases of thromboembolic etiology, such as in arteritic AION, the risk of a fast deterioration of the other eye is high (Hayreh, 2011). Third, in classic NA-AION patients, compared to age-matched controls, no increased incidence of cranial embolic events was observed (Kosmorsky, Straga, Knight, Dagirmanjian, & Davis, 1998). However, in our patient, previous cerebral infarctions were observed by CT and confirmed the presence of thromboembolic disease. Fourth, the extremely high estradiol levels in our patient were likely to be thrombogenic and to increase arterial disease. In a large population based study, women using contraceptive pills with higher estradiol dosage had a higher risk of arterial disease (myocardial infarction and stroke) compared to women using lower estradiol dosage (Lidegaard, Løkkegaard, Jensen, Skovlund, & Keiding, 2012). Finally, the time course of development of both non-arteritic ischemic optic neuropathies after start of high dose estrogen treatment is suggestive for thrombo-embolic etiology.

Management of NA-ION has been a highly controversial subject (Hayreh, 2009). Treatment with high dose systemic corticosteroids was found to improve visual acuity and visual field (Hayreh & Zimmerman, 2008b) although others recommended against this approach (Biousse, 2010). Given the possible detrimental effects of high dose corticosteroid treatment on acute cerebral ischemia and glucose metabolism, we decided not to initiate this therapy in a diabetic patient with several cardiovascular risk factors who experienced a stroke very recently. Besides corticosteroid treatment, it is recommended to reduce all possible cardiovascular risk factors (Hayreh, 2009).

NA-ION is an arterial disease and other arterial thromboses, such as transient ischemic attack, stroke, and myocardial infarction, have been reported during cross-sex hormone administration but it is currently not well-known whether estrogen treatment increases arterial morbidity and mortality in transsexual women (Gooren, 2011). Some studies found an increase in cardiovascular mortality (Dhejne et al., 2011) or morbidity compared to the general population whereas others did not (Van Kesteren, Asscheman, Megens, & Gooren, 1997).

Both oral contraceptives in premenopausal and hormone replacement therapy in postmenopausal women are known to

increase the risk for cardiovascular diseases, including cerebrovascular diseases (Sare, Gray, & Bath, 2008). Other cardiovascular risk factors, such as smoking, hypercholesterolemia, hypertension, and type 2 diabetes, play an even more important role (Lindenstrøm, Boysen, & Nyboe, 1993). It is advised that cardiovascular risk factors should be monitored and treated in transsexual persons before initiation of cross-sex hormone treatment (Hembree et al., 2009); however, no recommendations are available on a dosage reduction in sex hormone treatment in patients with cardiovascular risk factors.

In conclusion, we presented a case of bilateral non-arteretic anterior ischemic optic neuropathy possible associated to excessive estrogen therapy in a transsexual woman with co-morbidities. It is highly likely that these high estradiol levels were related to the cerebrovascular thrombosis and also played a role in development of the bilateral sequential NA-ION.

Acknowledgments K. W. is funded by the Special Research Fund of Ghent University (01D20711).

References

Biousse, V. (2010). Steroids should not be offered to patients with nonarteritic anterior ischemic optic neuropathy. *Journal of Neuro-Ophthalmology, 30*, 194–195.

Dhejne, C., Lichtenstein, P., Boman, M., Johansson, A., Langström, N., & Landén, M. (2011). Long-term follow-up of transsexuals persons undegoing sex reassignment surgery: Cohort study in Sweden. *PloS One, 6*(2), e16885. doi:10.1371.

Gooren, L. (2011). Care of transsexual persons. *New England Journal of Medicine, 364*, 1251–1257.

Gooren, L. J., Giltay, E. J., & Bunck, M. C. (2008). Long-term treatment of transsexuals with cross-sex hormones: Extensive personal experience. *Journal of Clinical Endocrinology and Metabolism, 93*, 19–25.

Hayreh, S. (2009). Ischemic optic neuropathy. *Progress in Retinal and Eye Research, 28*, 34–62.

Hayreh, S. (2011). Management of ischemic optic neuropathies. *Indian Journal of Ophthalmology, 59*, 123–136.

Hayreh, S., & Zimmerman, M. B. (2008a). Nonarteriticic anterior ischemic optic neuropathy: Clinical characteristics in diabetic patients versus nondiabetic patients. *Ophthalmology, 115*, 1818–1825.

Hayreh, S., & Zimmerman, M. B. (2008b). Non-arteritic anterior ischemic optic neuropathy: Role of systemic corticosteroid therapy. *Graefes Archive for Clinical and Experimental Ophthalmology, 246*, 1029–1046.

Hembree, W. C., Cohen-Kettenis, P., Delemarre-van de Waal, H. A., Gooren, L. J., Meyer, W. J., Spack, N. P., … Montori, V. M. (2009). Endocrine treatment of transsexual persons. An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism*, *94*, 3132–3154.

Johnson, N., & Arnold, A. C. (1994). Incidence of nonarteritic and arteritic anterior ischemic optic neuropathypopulation-based study in the state of Missouri and Los Angeles County, California. *Journal of Neuro-Ophthalmology, 14*, 38–44.

Kosmorsky, G., Straga, J., Knight, C., Dagirmanjian, A., & Davis, D. A. (1998). The role of transcranial Doppler in nonarteritic ischemic optic neuropathy. *American Journal of Ophthalmology, 126*, 288–290.

Lidegaard, Ø., Løkkegaard, E., Jensen, A., Skovlund, C., & Keiding, N. (2012). Thrombotic stroke and myocardial infarction with hormonal contraception. *New England Journal of Medicine, 366*, 2257–2266.

Lindenstrøm, E., Boysen, G., & Nyboe, J. (1993). Life style factors and risk of cerebrovascular disease in women: The Copenhagen City Heart Study. *Stroke, 24*, 1468–1472.

Newman, N. J., Scherer, R., Langenberg, P., Kelman, S., Feldon, S., Kaufman, D., & Dickersin, K. (2002).The fellow eye in NAION: Report from the ischemic optic neuropathy decompression trial follow-up study. *American Journal of Ophthalmology*, *134*, 317–328.

Sare, G., Gray, L., & Bath, P. (2008). Association between hormone replacement therapy and subsequent arterial and venous vascular events: A meta-analysis. *European Heart Journal, 29*, 2031–2041.

Van Kesteren, P. J., Asscheman, H., Megens, J. A., & Gooren, L. J. (1997). Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clinical Endocrinology, 47*, 337–342.

Wierckx, K., Mueller, S., Weyers, S., Van Caenegem, E., Roef, G., Heylens, G., & T'Sjoen, G. (2012). A long-term evaluation of cross-sex hormone treatment in transsexual persons. *Journal of Sexual Medicine*, *9*, 2641–2651.